accompanying "marked up" version pursuant to 1.121):

Sub C1 B1

1. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant ~~mouse~~ which has a degenerated liver; and

b. ~~transplanting~~ xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes infected with at least one compatible mammalian hepatitis virus.

Sub C2 B2

8. (Amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse having a ~~degenerated liver~~ parenchyma repopulated with transplanted xenogenic ~~mammalian~~ hepatocytes, said xenogenic mammalian hepatocytes infected with a compatible mammalian hepatitis virus.

REMARKS

Claims 1 and 8 have been amended to more particularly point out that the xenogenic mammalian hepatocytes recited in the claims are infected with a compatible mammalian hepatitis virus. Support for the amendments is found in the specification at page 5, lines 11-13 and in original claims 2, 3, 9 and 10. Accordingly, amended claims 1 and 8 do not contain new matter.

FORMAL DRAWINGS

Applicants acknowledge the Draftsman's objections to the drawings. Formal drawings will be filed upon indication of allowable claims.

CLAIM REJECTIONS

Rejections under 35 U.S.C.§112, first paragraph. Claims 1-5, 8-12, 15-21, 24-33, 35 and 36 are rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the

specification does not enable any person skilled in the art to which the claims pertain to make and use the invention commensurate in scope with the claims. The Examiner alleges in particular that the specification does not reasonably provide enablement for any and all chimeric immunetolerant mice having a degenerated liver and comprising xenogenic mammalian hepatocytes which can be infected with a compatible hepatitis virus, and methods of making and using the same chimeric immunetolerant mice. Applicants respectfully traverse.

The Examiner alleges that the specification is not enabling for every immunetolerant mouse. Applicants respectfully traverse. All of the information required to practice the full scope of the present claims is available to those skilled in the art within the four corners of the present specification.

Applicants have disclosed the RAG2 mouse as an example of an immunetolerant mouse for use in the invention. At the time the invention was made, it was well known that a plurality of independent genetic lesions could lead to immunetolerant mice, with properties virtually identical to RAG2 mice. The present specification specifically discloses that immunetolerant mice deficient in B and T cells are suitable for use in the invention. Several examples of immunetolerant mice are specifically disclosed, such as RAG2 knockout mice, nude mice, RAG1 knockout mice and SCID mice (*see* page 8, lines 18-20). These types of immunetolerant mice were well known and readily available to one of ordinary skill in the art at the time the invention was made.

In further support of their argument, Applicants submit herewith an excerpt from a textbook reference (Janeway et al., "The Immune System in Health and Disease", Third Edition, pp. 3:19-20 and 10:19, 1997, attached at Tab 1). Janeway et al. describe the RAG1, RAG2 and

scid genes, including their biochemical functions. Janeway et al. disclose that the RAG1, RAG2, and *scid* genes are independent loci. Janeway et al. further disclose that mice with either of the RAG genes knocked out suffer a compete block in primary lymphocyte development (*see* top of p. 3:20) and that *scid* mice make only trivial amounts of immunoglobulin or T-cell receptors (*see* p. 3:20, second paragraph). Accordingly, Janeway et al. (filed prior to the earliest claimed priority date of the present application) teach that mice with mutations in any of RAG1, RAG2 or *scid* genes are deficient in B and T cells (*see* 10:19, third paragraph), i.e., these mice are immunetolerant.

With regard to enabling repopulation of any immunetolerant liver with xenographic transplants, at the time the invention was made, one of ordinary skill in the art of immunology or transplant biology would immediately appreciate that any mouse incapable of producing mature B and T cells would be unable to recognize foreign antigens and would therefore be unable mount an immune response against or reject foreign cells. Accordingly, at the time the invention was made, it was well accepted in the field that any immunetolerant mouse liver will accept foreign cells from any species. The Examiner has provided documentation to this effect with a textbook reference (Kuby, J., *Immunology*, second edition, 1994) that teaches SCID mice, due to their lack of mature B and T cells fail to reject transplanted xenogenic (e.g., human) tissue.

The Examiner also alleges that the specification is enabling only for an immunetolerant mouse in which liver degeneration is caused by the uPA transgene. Applicants traverse. The specification discloses that a "degenerated liver" is a diseased liver having compromised biochemical function which leads to either hepatocyte death and/or inability to

replicate (*see* page 8, lines 8-14). At the time the invention was made, it would have been routine for one of ordinary skill in the art to obtain degenerated liver using any established protocol, in addition to uPA transgene expression disclosed by Applicants. It would further have been routine for the one of ordinary skill in the art to repopulate degenerated livers with exogenous congenic hepatocytes.

Two such procedures for preparing animals with degenerated liver and repopulating the degenerated liver with congenic hepatocytes are disclosed in the attached exhibits. Overturf et al. (Nature Genetics, 12:266-273, 1996, attached at Tab 2) disclose a procedure for obtaining degenerated liver in FAH-deficient mice followed by repopulating the degenerated liver with wild type congenic hepatocytes. Laconi et al. (American Journal of Pathology, 153:319-329, July 1, 1998, attached at Tab 3) disclose a procedure for repopulating normal rat liver with congenic hepatocytes following liver degeneration induced by exposure to an alkaloid, retrosine.

The procedures of Overturf et al. and Laconi et al. are practiced on immuno-competent animals. As such, these models are unsuitable for repopulation of degenerated liver with xenogenic hepatocytes. The teachings of the present disclosure, however, combined with standard genetic or biochemical procedures, would enable the skilled worker to make and use the invention with these methods of affecting liver degeneration and repopulation.

The Examiner concludes by alleging that the specification is only enabling for the use of uPA/RAG-2 mice with degenerated livers as recipients of transplanted xenogenic mammalian hepatocytes. Applicants respectfully traverse. The foregoing remarks establish that the specification is enabling for a broad range of immune tolerant mice and a broad range of

methods for causing liver degeneration in mice. At the time the invention was made, it was well within the state of the art to combine any genetic background that would lead to immunetolerance (e.g., RAG1, RAG2, *scid* or *nu*) with any genetic background that would lead to degenerated liver (e.g., uPA transgenic mice or FAH-deficient mice) by carrying out a standard two factor cross. The specification provides details of such a cross to obtain the uPa/RAG2 mouse (*see* p. 17, line 17 through page 18, line 11).

Hence, given the advanced state of the art of using immunetolerant mice, the advanced state of transgenic mouse technology, and the advanced state of the art of repopulating liver following liver degeneration caused by either genetic or chemical means, at the time the invention was made the ordinary skilled artisan would have found the present disclosure contained sufficient information to permit repopulating any immunetolerant mouse with liver degenerated by any means. No further information would have been required by those of ordinary skill in the art.

Finally, with regard to claim breadth (*see* Office Action at p. 6, middle paragraph), amended claims 1 and 8 are directed to a degenerated mouse liver, repopulated with xenogenic mammalian hepatocytes that are infected (either prior to or following transplantation) with a compatible hepatitis virus. Accordingly, the scope of the claims are commensurate with the specification, which teaches how to use the invention as a model for hepatitis.

In light of the foregoing arguments, Applicants respectfully submit that the specification enables the full breadth of the claims. Accordingly, Applicants request reconsideration of the claims and withdrawal of all rejections under 35 U.S.C.§112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph. Claims 1-14 are rejected as indefinite for failing to point out and distinctly claim the subject matter the Applicants regard as the invention. Independent claims 1 and 8 are rejected as indefinite for reciting that xenogenic mammalian hepatocytes are "capable of" being infected. In response, the phrase "capable of" has been deleted from amended claims 1 and 8. Amended claims 1 and 8 are now directed to xenogenic mammalian hepatocytes infected (either prior to or following transplantation) with a compatible hepatitis virus. Accordingly, it is respectfully submitted that amended claims 1 and 8, and all claims dependent thereon, are now definite. Reconsideration of the claims and removal of the rejection are believed to be in order.

Rejections under 35 U.S.C. §102. Claims 1-36 are rejected under 35 U.S.C. §102(a) as anticipated by Petersen et al. (Proc. Natl. Acad. Sci. USA 95:310-315, 1998). In response, without conceding any applicability of the cited reference, Applicants submit herewith a declaration of inventor Dr. Charles E Rogler, under 37 C.F.R. §1.132. The declaration states that Petersen et al. disclose the work of Dr. Rogler and Dr. Joerg Petersen. Dr. Petersen is not currently named as an inventor in this application. However, a petition to add Dr. Petersen as an inventor pursuant to 37 C.F.R. §1.48 is being submitted concurrently with this response. Petersen et al. therefore disclose the inventors' own work. Accordingly, Petersen et al. is not available as prior art under 102(a) against the instant claims. Applicants therefore request that all rejections of record under 102(a) be withdrawn.

Rejections under 35 U.S.C. §103. Claims 1-36 are rejected as obvious over Rhim et al. (Proc. Natl. Acad. Sci. USA 92:4942-4946, 1995) in view of Roggendorf et al. (Intervirology 38:100-112, 1995). The Examiner alleges that it would have been obvious to

arrive at the claimed invention by combining the chimeric immunetolerant mouse repopulated with rat hepatocytes, disclosed by Rhim et al., with the woodchuck hepatitis virus (WHV) model of infection, disclosed by Roggendorf et al. Applicants traverse.

The present claims are not obvious because there is no suggestion in the prior art that any benefit or advantage would be obtained by repopulating degenerated liver with transplanted xenogenic hepatocytes that are infected with a compatible hepatitis virus.

Each claim of claims 1-36 is directed to a chimeric immunetolerant mouse comprising a degenerated liver. In each of claims 1-36, the degenerated liver is repopulated with xenogenic hepatocytes infected with a compatible hepatitis virus. Rhim et al. do not disclose or suggest claims 1-36. At most, Rhim et al. can be construed to suggest that immunetolerant Alb-uPA mice provide a "tool" for studying hepatocellular biology and could "potentially" be used as a "model" for human liver disease. These suggestions are very broad and vague and of no practical value. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) Rhim et al. do not suggest any particular liver disease for which the Alb-uPA mouse may serve as a model. Nor do Rhim et al. even hint that degenerated liver in an immunetolerant mouse should be repopulated with xenogenic cells infected with any type of virus, much less a compatible hepatitis virus, as defined in the present claims.

The Examiner contends that the defects of Rhim et al. are cured by combination with Roggendorf et al. Applicants traverse. Roggendorf et al. merely teach the woodchuck system as a model for human hepatitis B infection. Roggendorf et al. are directed solely to the use of the woodchuck animal, woodchuck hepatocytes and woodchuck hepatitis virus.

Roggendorf et al. make no suggestion (either alone or in combination with Rhim et al.) to use woodchuck hepatocytes and WHV in a transgenic animal model of any kind. Nor do Roggendorf et al. suggest using WHV to infect an immunetolerant host of any kind. Accordingly, Roggendorf et al. make no suggestion to use woodchuck hepatocyte, or any other type of hepatocyte capable of being infected with hepadnavirus, as a xenogenic donor hepatocyte to repopulate degenerated liver in an immunetolerant mouse, such that the xenogenic donor hepatocytes are infected with a compatible hepatitis virus, as recited either directly or indirectly in each of claims 1-36. Accordingly, Roggendorf et al. make no suggestion, either alone or in combination with Rhim et al., to arrive at the claimed invention.

Applicants further traverse the obviousness rejections on the grounds that the prior art of record fails to provide the required motivation and suggestion of success that would lead one of ordinary skill in the art to combine the cited references. The Examiner contends that the motivation for combining the references is provided by an art recognized goal to develop treatments for human hepatitis and hepatocellular carcinomas, as suggested by Rhim et al. Applicants respectfully traverse. To explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it applies an obvious to try standard. *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)

Obvious to try is not a valid test of patentablility. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529, 1531 (Fed. Cir.1988) *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir.1986), *cert. denied,* 480 U.S. 947 (1987)

The Examiner bears the burden of establishing a prima facie case of obviousness

based upon the art. Both the suggestion of making the present invention, and a reasonable expectation of success must be founded in the prior art, not in Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529, 1531 (Fed. Cir.1988) Applicants respectfully submit that neither of these criterion has been met.

At best, the prior art provides only general guidance for the utility of immunetolerant Alb-uPA as a repository for human hepatocytes, as reagent for carcinogenicity **or** (emphasis added) as models for human liver disease. The cited prior art fails to provide any specific reasonable motivation or expectation of success for creating an immunetolerant mouse which has a degenerated liver and transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver where the xenogenic mammalian hepatocytes are infected with at least one compatible mammalian hepatitis virus (nor even the desirability of creating such a mouse).

In contrast to the prior art, the present invention recognizes the desirability of determining the characteristics of hepatitis B infection in the absence of B and T cells. The immunetolerant mouse of the present claims provides such a system. The present invention also recognizes that repopulation of degenerated liver in immunetolerant mouse with rat hepatocytes (as disclosed in the prior art of record) has inherent disadvantages because rat cells are not natural hosts for hepadnavirus and cannot be infected by natural mechanisms with any of the known hepadnaviruses. After recognizing both the advantages and limitations of the immunetolerant mouse-rat hybrid system, the present specification discloses an immunetolerant mouse with degenerated liver that is repopulated with hepatocytes that are a natural host for infections with a compatible hepatitis virus.

In light of the foregoing discussion, Applicants respectfully submit that the Examiner has used the present disclosure and hindsight as the rationale to combine the prior art of record. This is an impermissible rationale for rejecting the claims as obvious. *In re Fritch,* 972 F2d. 1260, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992)

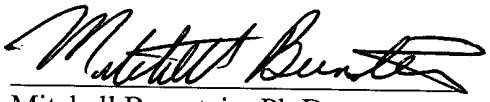
For all the reasons given above, it is respectfully submitted that claims 1-36 are not obvious over the cited art. Accordingly, removal of all rejections under 35 U.S.C.§103 and reconsideration of the claims is respectfully requested.

CONCLUSION

Applicants respectfully request entry of the above amendments and remarks.

In view of the above amendments and remarks, this application is believed to be in condition for allowance, which is earnestly solicited.

Respectfully submitted,



Mitchell Bernstein, Ph.D.
Reg. No. 46,550
Agent for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED MAR 15 2001 OFFICE OF PETITIONS

In re application of: Charles E. ROGLER

Serial No.: 09/344,189 Art Unit: 1632

Filed: June 24, 1999 Examiner: P. Paras, Jr.

For: **CHRONIC HEPATITIS VIRUS INFECTION AND CLONAL HEPATOCELLULAR CARNCINOMA IN MOUSE REPOPULATED WITH LIVERS**

MARK-UP FOR AMENDMENT OF MARCH 12, 2001
PURSUANT TO 37 C.F.R. § 1.121

March 12, 2001

IN THE CLAIMS

1. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse which has a degenerated liver; and

b. transplanting xenogenic mammalian hepatocytes [capable of being infected with at least one compatible mammalian hepatitis virus] to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes infected with at least one compatible mammalian hepatitis virus.

8. (Amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse having a degenerated liver parenchyma repopulated with transplanted

xenogenic mammalian hepatocytes [that are capable of being], said xenogenic mammalian hepatocytes infected with a compatible mammalian hepatitis virus.